[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA AND THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES]

The Isomeric 3-Oxa- and 3-Thiagranatanin-7-ols and Their Derivatives; Reduction of Bicyclic Amino Ketones Related to Tropinone[1,2]

CHARLES L. ZIRKLE,[3,4] FRED R. GERNS,[5] ALEX M. PAVLOFF,[3] AND ALFRED BURGER

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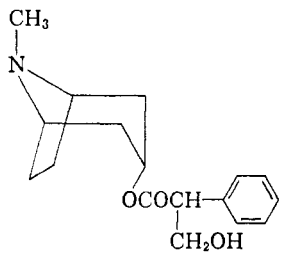
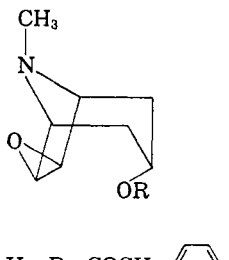
A pseudopelletierine analog, 9-methyl-3-oxagranatanin-7-one (III), was prepared by the Robinson-Schöpf condensation of oxydiacetaldehyde, methylamine, and acetonedicarboxylic acid. Reduction of this ketone and its 3-thia analog (V) by various methods gave epimeric 9-methyl-3-oxa- and 9-methyl-3-thiagranatanin-7α- and 7β-ols (IVA–IVB; VIA–VIB). In contrast to the related ketones tropinone (IX) and "homopseudopelletierine" (XI), which are reported to yield high proportions of equatorial alcohols upon lithium aluminum hydride reduction, compounds III, V, and pseudopelletierine (VII) were found to form predominantly the axial epimers under these conditions. Esters and ethers of the amino alcohols IV, VI and VIII and related compounds were prepared for pharmacological evaluation.

Although the central nervous system effects of atropine (I) and its congeners have long been recognized, the clinically useful actions of these drugs upon the autonomic nervous system have received most attention. Most of the numerous analogs of the alkaloid have been synthesized in attempts to find compounds having the same antispasmodic effects on the gastrointestinal tract but showing to a lesser degree the side effects possessed by atropine. Recently, however, in the course of extensive reinvestigations of drugs by modern psychopharmacological and neurophysiological techniques, interest has refocused on the central nervous system actions of these agents,[6,7] some of which, *e.g.*, diethylaminoethyl benzilate (benactyzine), have been used in the treatment of certain mental disorders.[8]



I



IIa. R = COCH(CH$_2$OH)–C$_6$H$_5$

b. R = H

As a parasympatholytic agent, scopolamine (IIa) is considerably more potent than, although qualitatively similar to, atropine in some of its anticholinergic effects.[9] Furthermore, the former drug appears to differ qualitatively as well as quantitatively from the latter in its action upon the central nervous system. Although there are conflicting reports on the central effects of the two agents in lower animals, in man scopolamine, in therapeutic doses, produces sedative effects while atropine shows an excitatory action.[6,10]

With this relationship between structure and biological activity in mind, we undertook the syntheses of some atropine analogs which resemble scopolamine more closely than those prepared heretofore for study as potential pharmacological and psychopharmacological agents. The susceptibility of IIa and scopine (IIb) to undergo rearrangement to scopoline under very mild conditions[11] has limited the number of scopolamine analogs which could be prepared.[12]

For our studies we selected derivatives of the isomeric 9-methyl-3-oxagranatanin-7α- and 7β-ols (IVA and IVB, Chart I),[13] which may be viewed as

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(3) Smith Kline and French Laboratories.

(4) To whom inquiries concerning this paper may be addressed.

(5) Present address: Burroughs Wellcome and Co., Tuckahoe, N. Y.

(6) E. Jacobsen, *J. Pharm. and Pharmacol.*, 10, 273 (1958).

(7) H. Riley and A. Spinks, *J. Pharm. and Pharmacol.*, 10, 657 (1958); *J. Pharm. and Pharmacol.*, 10, 721 (1958).

(8) E. Jacobsen and E. Sonne, *Acta Pharmacol. Toxicol.*, 11, 135 (1955).

(9) A. Herxheimer, *Brit. J. Pharmacol.*, 13, 184 (1958).

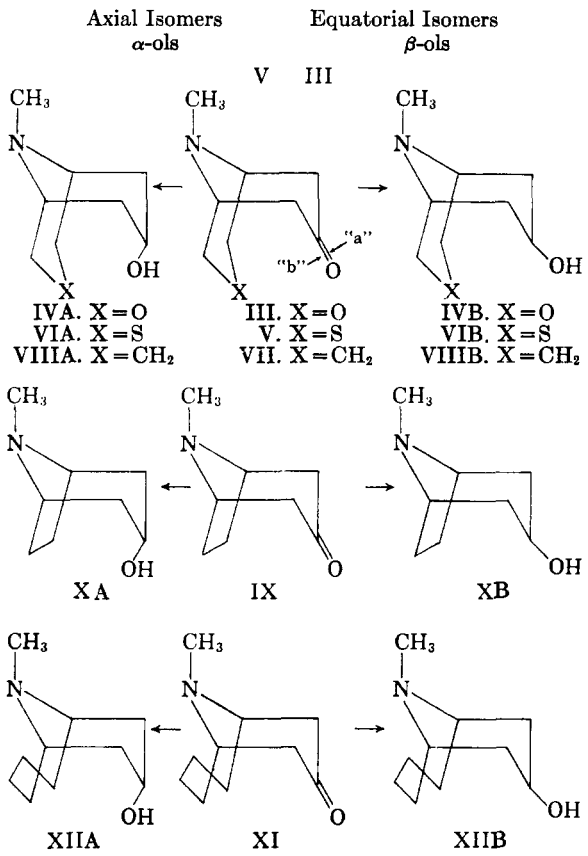
(10) V. G. Longo, *J. Pharmacol. Exptl. Therap.*, 116, 198 (1956); A. G. Karczmar and J. P. Long, *J. Pharmacol. Exptl. Therap.*, 123, 230 (1958); F. H. Meyers and B. E. Abreu, *J. Pharmacol. Exptl. Therap.*, 104, 387 (1952).

(11) R. Willstätter and E. Berner, *Ber.*, 56, 1079 (1923); G. Fodor, *Nature*, 170, 278 (1952); J. Meinwald, *J. Chem. Soc.*, 712 (1953).

(12) Quite recently a few synthetic esters and ethers of scopine have been reported. K. Zeile and A. Heusner, *Arch. Pharm.*, 292, 238 (1959); Belgian Patent 571,253 (1958).

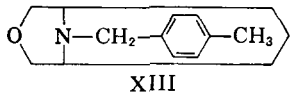
(13) A study of a Courtauld molecular model of IV, which contains a 1,3-fused morpholine-piperidine system, suggests less steric repulsion in the chair-chair form as shown, from which it may be inferred that this conformation is probably the most favored one. For conclusions concerning the conformation of the piperidine ring in related bicyclic amines, see N. J. Leonard, D. F. Morrow, and M. T. Rogers, *J. Am. Chem. Soc.*, 79, 5476 (1957), and references therein; for discussion of the conformation of morpholine, see M. Aroney and R. J. W. Le Fèvre, *Proc. Chem. Soc., London*, 82 (1958).

CHART I



being derived from scopine by opening of the unstable oxirane ring between C^6 and C^7.[14] For biological comparison with these compounds derivatives of the corresponding thia analogs, VI, and 9-methylgranatanin-3-ols (VIII) were also prepared.[15]

A 3-oxagranatanine derivative was first prepared by von Braun[16] who reported the synthesis of "*N*-*p*-methylbenzylmorphopiperidine" (9-*p*-methylbenzyl-3-oxagranatanine) (XIII). The first 3-thiagranatanine derivative to be reported was "thiatropinone" (9-methyl-3-thiagranatanin-7-one) (V), used as an intermediate in this work, which Robinson prepared in the course of further studies of his tropinone synthesis.[17]



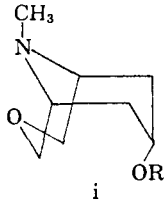
XIII

While the present studies were in progress our results were anticipated by Jerchel and Weidmann[18] who announced the synthesis of one isomer of each of the two amino alcohols IV and VI and a few esters of these prepared for pharmacological evaluation. In our work a more suitable synthetic approach than that used by these authors was followed; both isomers of IV and VI were obtained and the configurations of these were established. Thus, our results considerably extend those of these workers.

To obtain the two isomers of 9-methyl-3-oxagranatanin-7-ol (IVA and IVB) and of 9-methyl-3-thiagranatanin-7-ol (VIA and VIB), we reduced the corresponding ketones by various methods since the ratio of epimeric alcohols obtained in the reduction of cyclic and polycyclic ketones depends greatly upon the nature of the reducing agent and the conditions of the reduction.[19] In Table I the results of the reductions of III and V are summarized and compared with data in the literature on the reductions of the closely related ketones VII, IX, and XI (Chart I).

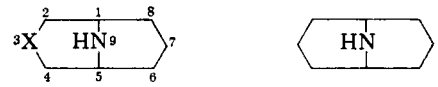
Upon catalytic hydrogenation and reduction by sodium and alcohols the three bicyclic amino ketones VII, IX, and XI follow the rules which generally predict the stereochemistry of reduction of other 6-membered cyclic and polycyclic ketones.[19-25] The former method in most cases, par-

(14) If the chair-chair conformation of VA is most favored (see footnote 13), this compound and its derivatives may not bear a close spatial relationship to scopolamine, in which the oxirane oxygen is directed toward the nitrogen. However, the protonated (ammonium) form of these compounds in interacting with drug-receptors in biological systems may possibly assume other conformations, *e.g.*, boat-chair form i, which more closely resemble scopolamine.



i

(15) According to *Chem. Abstr.* nomenclature, the ring systems from which these and other compounds discussed in this paper are derived are designated 3-ox- and 3-thia-9-azabicyclo[3.3.1]nonanes (formula ii).



ii iii

For the sake of brevity we prefer to name them as oxa- and thia-analogs of granatanine (iii), numbering the ring positions as indicated in formula ii. In naming the isomeric alcohols IV, VI, and VIII, we have adopted the nomenclature introduced by G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953), to indicate the configurations of isomers in the closely related tropanol series. With the nitrogen bridge as point of reference, substituents on the same side of the general plane of the piperidine ring are designated as β while those on the opposite side are designated as α.

(16) J. von Braun and W. Leistner, *Ber.*, **59**, 2323 (1926).

(17) B. K. Blount and R. Robinson, *J. Chem. Soc.*, 2485 (1932).

(18) D. Jerchel and H. Weidmann, *Ann.*, **607**, 126 (1957).

(19) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(20) W. Hückel, M. Maier, E. Jordan, and W. Seeger, *Ann.*, **616**, 46 (1958).

(21) J. H. Brewster, *J. Am. Chem. Soc.*, **76**, 6361 (1954).

(22) E. G. Peppiatt and R. J. Wicker, *Chem. & Ind. (London)*, 747 (1955).

(23) R. J. Wicker, *J. Chem. Soc.*, 2165 (1956).

TABLE I

THE PROPORTIONS OF ISOMERS IN THE REDUCTION PRODUCTS OF BICYCLIC AMINO KETONES RELATED TO TROPINONE

Ketone (Chart I)	Reducing Agent	Alcohol Products, % Axial (α-ols)	Equatorial (β-ols)
III	H_2–Ni(RuO_2)	>85[a]	
	$LiAlH_4$	>85[a]	
	Na-pentanol		>80[a]
V	$LiAlH_4$	>85[a]	
	Na-pentanol		>75[a]
VII	H_2–Ni(PtO_2)	Predominantly[28,29]	
	$LiAlH_4$	>85[a]	
	Na-ethanol		Predominantly[28,29]
IX	H_2–PtO_2	Predominantly[27]	
	$LiAlH_4$	41–45[31]	54–57[31]
	Na-isobutanol	7–10[31]	84–88[31]
XI	H_2–Ni	Predominantly[30]	
	$LiAlH_4$		>80[b]
	Na-ethanol		Predominantly[30]

[a] Estimated (see Experimental part). [b] Estimated from data of Alder *et al.*[30] (see footnote 32).

ticularly in acid medium, yields a mixture of epimeric alcohols containing a high percentage of the axial isomer[19–23]; the latter method seems invariably to give a preponderance of the thermodynamically more stable equatorial isomer.[19,20]

Thus tropinone (IX) and its higher ring-homologs, pseudopelletierine (VII) and "homopseudopelletierine" (XI),[26] all upon catalytic hydrogenation add hydrogen chiefly on side "a" of the carbonyl (as shown in III, V, and VII) to give mostly the axial isomers (α-ols) XA,[27] VIIIA,[28,29] and XIIA.[30] On the other hand, reduction of these ketones by sodium and alcohols results in the predominant formation of the equatorial alcohols (β-ols) XB,[31] VIIIB,[28,29] and XIIB.[30] In the present work the oxaketone (III) was found to behave in a manner analogous to that of ketones VII, IX, and XI under the two types of reduction conditions. Hydrogenation of III over Raney nickel in alcohol or ruthenium oxide in acetic acid yielded chiefly 9-methyl-3-oxagranatanin-7α-ol (IVA), m.p. 144–146°. The infrared spectra of the crude products indicated that very little of the β-ol IVB was present and no attempt was made to isolate it. The latter isomer, 9-methyl-3-oxagranatanin-7β-ol (IVB), m. p. 111.5–113°, was readily obtained by reduction of III with sodium and 1-pentanol and by epimerization of IVA in the presence of aluminum isopropoxide. That IVB was obtained under these conditions indicated that it was the more stable equatorial isomer. The configurations of the epimeric alcohols were established conclusively by methods used in analogous studies in the tropanol and granataninol series (see below).

Because of the presence of sulfur in the thiaketone no attempt was made to reduce the latter by catalytic hydrogenation; sodium-pentanol reduction, however, yielded one epimer of 9-methyl-3-thiagranatanin-7-ol, presumably the equatorial isomer VIB (β-ol), m.p. 116.5–117°.

Studies were also made of the reduction of the oxa- and thiaketones with lithium aluminum hydride. The stereochemical course of reduction of cyclic ketones with this reagent and other complex metal hydrides is not as predictable as that of reductions by the methods discussed above. In general, sterically unhindered ketones with lithium aluminum hydride yield predominantly equatorial alcohols while highly hindered ketones under these conditions give mainly axial alcohols. However, in the case of less hindered ketones prediction of the major product is more difficult.[24,25] Beckett and coworkers[31] in a quantitative study of the reduction of tropinone (IX) by sodium and alcohols and by metal derivatives found that the lithium aluminum hydride reduction product contained 41–45% of the axial alcohol XA and 54–57% of the equatorial epimer XB. On the other hand Alder[30] obtained a product from the lithium aluminum hydride reduction of "homopseudopelletierine" (XI) that appeared to consist of 80% or more of the equatorial alcohol XIIB.[32]

In the present study, lithium aluminum hydride reduction of the oxa- and thiaketones (III and V) was found to follow a stereochemical course considerably different from that observed in the reductions of IX and XI—a course leading predominantly to the axial isomers (IVA and VIA).

(24) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

(25) K. D. Hardy and R. J. Wicker, *J. Am. Chem. Soc.*, **80**, 640 (1958).

(26) 10-Methyl-10-azabicyclo[4.3.1]decan-8-one.

(27) L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946).

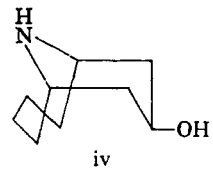
(28) K. Alder and H. A. Dortmann, *Ber.*, **86**, 1544 (1953).

(29) W. H. Hartung and S. M. Gadekar, *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 715 (1953).

(30) K. Alder, H. Wirtz, and H. Koppelberg, *Ann.*, **601**, 138 (1956).

(31) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(32) These authors did not quantitatively examine the reduction product which was an oil. However, demethylation of this material gave in 88% yield a sharply melting (m.p. 141°) *nor* base iv which was shown by the method of



iv

acyl migration (*cf.* ref. 35) to have the configuration shown (OH equatorial).

With this reagent the oxaketone yielded mainly the same alcohol, m.p. 144–146°, obtained by catalytic hydrogenation, and the thiaketone gave as the chief product an alcohol (VIA), m.p. 108–110°, different from that obtained by sodium-pentanol reduction. In the latter case, a small amount of the isomer (VIB), m.p. 116.5–117°, originally obtained by sodium-pentanol reduction, was isolated by chromatography of the filtrates from VIA. The configurations of VIA and VIB were assigned by analogy to those of the corresponding alcohols obtained by lithium aluminum hydride and sodium-pentanol reductions of the oxaketone.

Although the reduction mixtures were not assayed quantitatively for isomer content, the infrared spectra and other properties of the crude products suggested that they contained >85% of the α-ols (see Experimental).

Jerchel and Weidmann[18] also reduced the oxa- and thiaketones III and V with lithium aluminum hydride and obtained the α-ols IVA and VIA. However, these authors did not study other methods of reduction and assigned the β-configuration to the products by an analogy based on an erroneous report[31,33] that tropinone (IX) upon reduction with this agent yielded exclusively the β isomer (XB).

Although pseudopelletierine (VII) had been reduced catalytically and by sodium and alcohols, its reduction by lithium aluminum hydride has not been reported. We therefore reduced this ketone with the latter reagent to compare the alcohol product with those obtained by similar reduction of the oxa- and thiaketones. As in the latter cases we found that VII yielded predominantly the α-ol VIIIA.

Although our data on the reduction of these ketones are only qualitative, we believe that our results taken with those of Beckett[31] and of Alder[30] permit arrangement of members of this series of ketones in the following order according to the degree to which they yield axial alcohols (α-ols) upon lithium aluminum hydride reduction: 9-methyl-3-oxagranatanin-7-one (III), 9-methyl-3-thiagranatanin-7-one (V), pseudopelletierine (VII) >tropinone (IX) >"homopseudopelletierine" (XI).

According to current concepts, reviewed by Beckett and co-workers[31] in interpreting the results of their study of the reduction of tropinone, the ratio of axial to equatorial alcohols obtained from cyclic ketones is determined by: (1) the degree of steric hinderance operating between the ketone and the reducing agent (kinetic factor) and (2) the relative stabilities of the two alcohols that are ultimately formed (thermodynamic factor). With the piperidone ring of tropinone in the chair conformation the kinetic factor in the reduction favors formation of the axial alcohol XA since the reducing agent can approach the less hindered side "a" of the carbonyl (see formulas in Chart I) more readily than side "b" which is hindered by the ethylene bridge. The net result from operation of both of these factors is a ratio of axial to equatorial alcohol of about 45:55 instead of about 10:90 which would be expected if the reaction were governed entirely by the thermodynamic factor.[31]

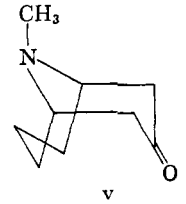
A possible explanation for the high ratios of axial to equatorial products obtained in the lithium aluminum hydride reductions of ketones III, V, and VII is that the three-atom bridge of these ketones (in the chair-chair conformation) hinders the approach of reducing agent at side "b" of the carbonyl more than does the ethylene bridge in tropinone with the result that attack from side "a" is even more favored than it is in the case of the latter ketone. On the other hand, in "homopseudopelletierine" (XI), the four-atom bridge, which is part of a seven-membered ring, being more flexible than either the two-atom or three-atom bridge, permits the ketone to assume conformations in which side "b" of the carbonyl is more easily accessible to the reducing agent than it is in the four related ketones. As a consequence the thermodynamic factor plays the dominant role in determining the course of the lithium aluminum hydride reduction of this compound, resulting in the equatorial alcohol as the predominant product.

While a comparison of molecular models of these ketones in the chair-chair form[34] supports this interpretation of the results, quantitative data on the ratios of isomeric alcohols present both in their lithium aluminum hydride reduction products and in mixtures of the epimers at equilibrium is necessary before definite conclusions concerning the relative importance of the thermodynamic and kinetic factors involved in these reductions may be drawn.

Confirmation of the configurations assigned to the epimeric 3-oxagranatanin-7-ols according to the concepts of conformational analysis was obtained by the methods of acyl migration and tetrahydrooxazine formation—procedures utilized in similar

(33) R. Mirza, *Nature*, 170, 630 (1952).

(34) However, see Leonard and co-workers (ref. in footnote 13) who found from a study of a pseudopelletierine model that possibly less steric repulsion occurred in the boat-chair conformation, v. These authors tentatively concluded that conformations related to v may be the more favored forms of the ketone. Our study of models (Courtauld) also suggested that v may be favored but we did not observe any major differences in degree of steric repulsion between the chair-chair and boat-chair forms of either this ketone or the oxa- and thiaketones which would permit a firm conclusion concerning the more favored conformations of these compounds.



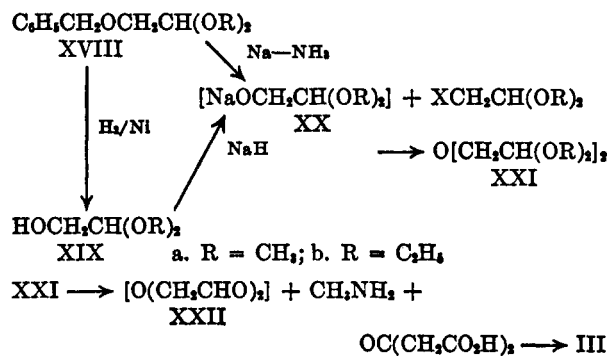
v

stereochemical studies in the closely related tropanol and granataninol series (Chart II).[28,35,36] The two isomers were oxidatively demethylated with alkaline permanganate to furnish the corresponding secondary-amino alcohols XIVB and XIVA. Methylation of the latter two derivatives by the Eschweiler method regenerated the original tertiary amino alcohols, proving that no change in the ring system had occurred in the demethylation process. The *N*-benzoyl derivative XVB of the *nor*-base XIVB obtained from IVB rearranged in anhydrous acid medium to the salt of the *O*-benzoyl derivative XVIB, while no change in the epimer XVA occurred under the same conditions. Furthermore, the *N*-benzoyl derivative XVB was regenerated from the salt of XVIB when the latter was treated with alkali. On the other hand, the epimeric *nor* ester XVIA under these conditions was hydrolyzed to the amino alcohol XIVA. As further proof of configurations, a crystalline *p*-nitrophenyltetrahydrooxazine derivative XVII formed readily when XIVB was treated with *p*-nitrobenzaldehyde, while only intractable tar was obtained from the reaction of XIVA with this aldehyde.

Since transient or permanent ring-closure through the amino and hydroxy groups of amino alcohols of this type can occur only in isomers having the *syn* configuration, these results establish that IVB is the β-ol and consequently IVA is the α-ol.

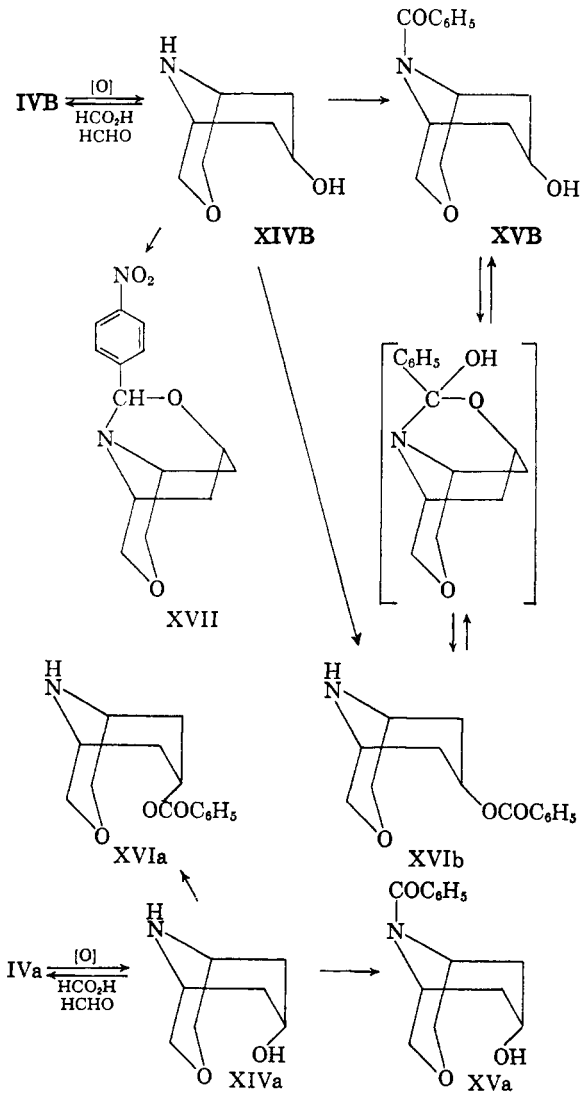
Physical and analytical data on the various amino alcohols prepared in this work and the salts and derivatives which served to characterize them are presented in Table II.

The synthesis of 9-methyl-3-oxagranatanin-7-one (III), the intermediate for the isomeric 3-oxagranataninols IVA and IVB, was accomplished by the Robinson-Schöpf condensation which required oxydiacetaldehyde (XXII) as starting material. Jerchel and Weidmann[18] state that they were unsuccessful in various attempts to prepare XXII and therefore were forced to use a longer route to the oxagranataninone III. We found, however, that the aldehyde could be readily obtained by the reaction sequence indicated below.



The hydroxyacetals XIXa and XIXb were obtained from the corresponding benzyloxyacetals XVIIIa and XVIIIb by either hydrogenolysis over Raney Nickel or debenzylation with sodium in liquid ammonia.[37] Treatment of the sodium derivative (XX) of XIXa or XIXb, prepared by the action of sodium hydride on the hydroxyacetals, with the appropriate haloacetal yielded the corresponding bis(dialkylacetal) of oxydiacetaldehyde XXIa or XXIb. The bisacetal XXIa was used in our large scale preparative work since it was obtained from the more readily available dimethylchloracetal. To obtain XXIa in quantity we found it convenient to treat the crude sodium derivative XXa formed in the sodium–liquid ammonia de-

CHART II

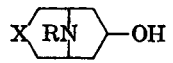


(35) G. Fodor and K. Nádor, *J. Chem. Soc.*, 721 (1953).
(36) A. Nickon and L. F. Fieser, *J. Am. Chem. Soc.*, 74, 5566 (1952).

(37) W. E. Parham and H. E. Reiff, *J. Am. Chem. Soc.*, 77, 6391 (1955). We are indebted to these authors for supplying their directions, prior to publication, for the preparation of the benzyloxyacetals and their conversion to hydroxyacetals by sodium-ammonia debenzylation.

TABLE II

3-OXA- AND 3-THIAGRANATANIN-7-OLS



Compound							Re-crystn.		Carbon, %		Hydrogen, %		Nitrogen, %	
No.	X	R	Config. of OH	Deriv.	Salt	M.P.	Solv.[a]	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
IVA	O	CH_3	α	—	—	144–146[b]	E	$C_8H_{15}NO_2$	61.12	61.06	9.62	9.59	8.91	8.88
					Picrate	276 dec.	C	$C_{14}H_{18}N_4O_9$	43.52	43.73	4.70	4.64	14.50	14.71
					Tartrate	183	B	$C_{12}H_{21}NO_8$	46.90	46.96	6.89	7.09	4.56	4.65
					CH_3Br	312 dec.	IB	$C_9H_{18}BrNO_2$	42.87	43.09	7.20	7.02		
					CH_3I	333	B	$C_9H_{18}INO_2$	36.13	36.17	6.06	6.38	4.68	4.74
				O-Benzoyl	—	76–78	F	$C_{15}H_{19}NO_3$	68.98	68.86	7.33	7.29		
XIVA	O	H	α	—	—	209–211	D	$C_7H_{13}NO_2$	58.72	58.72	9.15	9.08		
					Picrate	245–247 dec.	A	$C_{13}H_{16}N_4O_9$	41.93	41.66	4.33	4.49	15.05	15.44
XVA				*N*-Benzoyl	—	131–133	G	$C_{14}H_{17}NO_3$	67.99	68.18	6.93	7.13		
XVIA				*O*-Benzoyl	—	106–108	F	$C_{14}H_{17}NO_3$	67.99	68.07	6.93	7.07		
IVB	O	CH_3	β	—	—	111.5–113	D	$C_8H_{15}NO_2$	61.12	60.84	9.62	9.57	8.91	8.79
					Picrate	Indef.	AC	$C_{14}H_{18}N_4O_9$	43.52	43.27	4.70	4.74		
					CH_3I	300 dec.	AC	$C_9H_{18}INO_2$	36.13	36.16	6.06	6.19		
				O-Benzoyl	—	103.5–105	F	$C_{15}H_{19}NO_3$	68.98	68.82	7.33	7.10		
XIVB	O	H	β	—	—	131–132.5	H	$C_7H_{13}NO_2$	58.72	58.50	9.15	9.01		
					Picrate	206 dec.	HB	$C_{13}H_{16}N_4O_9$	41.93	41.93	4.33	4.30		
XVB				*N*-Benzoyl	—	143–144	D	$C_{14}H_{17}NO_3$	67.99	67.69	6.93	7.13	5.66	5.51
XVIB				*O*-Benzoyl	—	115–117	DE	$C_{14}H_{17}NO_3$	67.99	67.92	6.93	7.36		
VIA	S	CH_3	α	—	—	108–110[c]	DE	$C_8H_{15}NOS$	55.45	55.60	8.73	8.94	8.08	8.36
					Picrate	277 dec.	C	$C_{14}H_{16}N_4O_8S$	41.79	41.89	4.51	4.21	13.93	14.18
					CH_3I	314 dec	AC	$C_9H_{18}INOS$	34.29	34.41	5.76	5.97	4.44	4.64
VIB	S	CH_3	β	—	—	116.5–117	D	$C_8H_{15}NOS$	55.45	55.43	8.73	8.37		
					Picrate	265 dec.	C	$C_{14}H_{16}N_4O_8S$	41.79	41.83	4.51	4.59		
					CH_3I	297.5 dec.	B	$C_9H_{18}INOS$	34.29	34.46	5.76	6.12		

[a] Recrystallization solvents: A = ethanol, B = methanol, C = water, D = benzene, E = petroleum ether (b.p. 30–60°), F = ligroin, G = ether, H = ethyl acetate, I = butanone. [b] Lit.,[18] m.p. 140–142°. [c] Lit.,[18] m.p. 102–104°.

benzylation of XVIIIa directly with the chloroacetal.

By hydrolysis under mild conditions in dilute acetic or hydrochloric acid solutions, the oxydiacetals XXI were converted to oxydiacetaldehyde (XXII). Although the aldehyde was not isolated it was characterized as its bis(2,4-dinitrophenylhydrazone), obtained in almost quantitative yield from aqueous solutions of XXII.

The Robinson-Schöpf condensation of dialdehydes, amines, and acetone–dicarboxylic acid has been applied to the preparation of numerous analogs and homologs of tropinone (IX), including pseudopelletierine (VII) and 9-methyl-3-thiagranatanin-7-one (V). Optimum yields (80–89%) of tropinone have been reported to be obtained when the reaction of succinaldehyde, methylamine, and acetonedicarboxylic acid is carried out at *p*H 5–7.[38,39] Schöpf and Lehmann[38] found that the optimum *p*H for the formation of pseudopelletierine (VII) from glutaraldehyde in dilute solutions was also 5–7. These authors reported a 72% yield of VII under these conditions. Other workers,[28,40,41] however, found that *p*H 2.5–4 was optimal for preparing VII in moderately large quantities. In a careful study of the condensation reaction Cope and co-workers[40] obtained their best yields (45–57%) of pseudopelletierine working in this *p*H range.

Although we studied a number of variations of reaction conditions in preparing 9-methyl-3-oxa- and 9-methyl-3-thiagranatanin-7-ones (III and V) from oxydiacetaldehyde and thiodiacetaldehyde, respectively, we were not able to obtain either of these ketones in yields greater than 20–30%. In the case of the oxaketone (III), about the same yields were obtained throughout the range of *p*H 3–5.5. Since observation of the rates of carbon dioxide evolution and increase in *p*H in unbuffered solutions of the reactants indicated that the condensation occurred slowly below *p*H 5, most of our experiments were carried out in buffered solutions at *p*H 5–5.5.

On the other hand, the reaction leading to the thiaketone V proceeded rapidly at *p*H 3. Most of our experiments were carried out at this *p*H although about the same results were obtained at *p*H 4–5. We obtained about the same results when buffered solutions of reactants were held at approximately *p*H 3 by occasional addition of hydrochloric acid as when the reactions were run in buffered solutions at constant *p*H. In none of our experiments, most of which were carried out on a preparative scale, were we able to attain yields of V approaching that reported by Jerchel and Weidmann.[18] In a small scale preparation carried out in dilute solution these authors obtained a 52% yield of thiaketone.

A large amount of resinous material always formed in the reactions of oxydiacetaldehyde and of thiodiacetaldehyde, making isolation of the ketone products difficult. Cope and co-workers[40] encountered a similar problem in the preparation of pseudopelletierine.

Perhaps a more thorough investigation of reaction conditions than was made in this work would lead to considerable improvement in yields of the oxa- and thiaketones. However, the present results and the data of Cope and co-workers[40] suggest that oxydiacetaldehyde, thiodiacetaldehyde, and glutaraldehyde, all of which have three atoms separating the two carbonyl groups, undergo the condensation-cyclization reaction to form the 6-membered morpholine, thiomorpholine, and piperidine rings in the ketone products III, V, and VII less rapidly than does succinaldehyde to form the pyrrolidine ring in tropinone. As a result, considerable amounts of the former dialdehydes interact with methylamine to form resinous material as a major by-product of the reaction. In our study of the preparation of thiaketone V, we found that a solution of thiodiacetaldehyde and methylamine hydrochloride remained colorless for a considerable length of time, but that when the *p*H was increased to 3 it immediately darkened and a considerable amount of polymer separated within a period of two hours.

The esters and benzhydryl ethers of the oxa- and thiagranataninols and of the granataninols which were prepared for pharmacological study are listed with physical and analytical data in Table III. The syntheses of these compounds are described in the Experimental part. In addition, three miscellaneous derivatives XXXV, XXXVI, and XL in the oxagranatanine series were prepared by the reaction sequences shown below.

The configuration of XXXVI as pictured was assigned to this product by analogy to the carbinol of this configuration obtained from the reaction of tropinone with phenyl lithium.[31]

Reduction of 9-methyl-3-oxagranatanin-7-one oxime (XXXVII) with sodium and 1-pentanol furnished 7β - amino - 9 - methyl - 3 - oxagranatanine (XXXVIII). The configuration of the product was assigned on the basis of the fact that reduction of oximes, including tropinone oxime,[42,43] with sodium and alcohols follows the stereochemical course of the reduction of the corresponding ketones.[19] Treatment of XXXVIII with diphenylacetyl chloride gave the diphenylacetamide XL.

The comparative pharmacology of the compounds prepared in this work will be reported

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(39) G. Gál, I. Simonyi, and G. Tokár, *Magyar Kém. Folyóirat*, **61**, 74 (1955); *Chem. Abstr.*, **50**, 7115 (1956).
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(41) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950).
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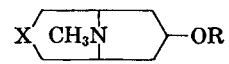
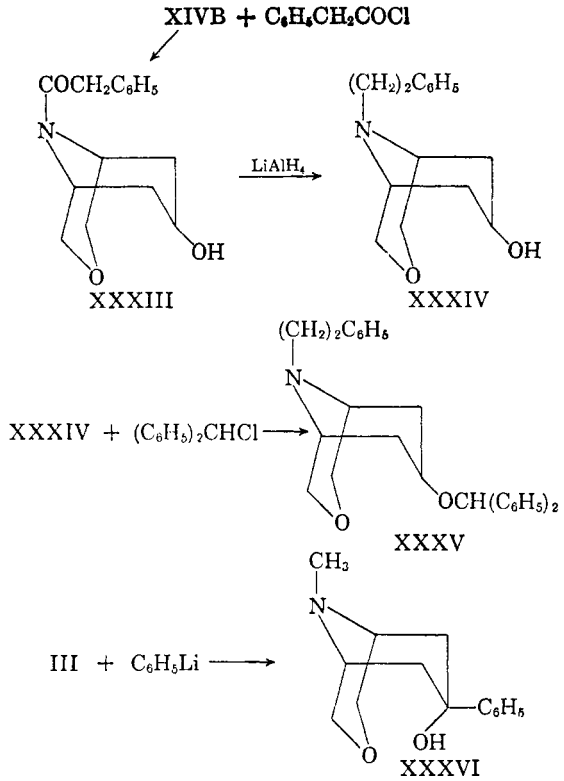
TABLE III

ESTERS AND BENZHYDRYL ETHERS OF 9-METHYL-3-OXA- AND 9-METHYL-3-THIAGRANATANIN-7-OLS AND OF 9-METHYLGRANATANIN-7-OLS

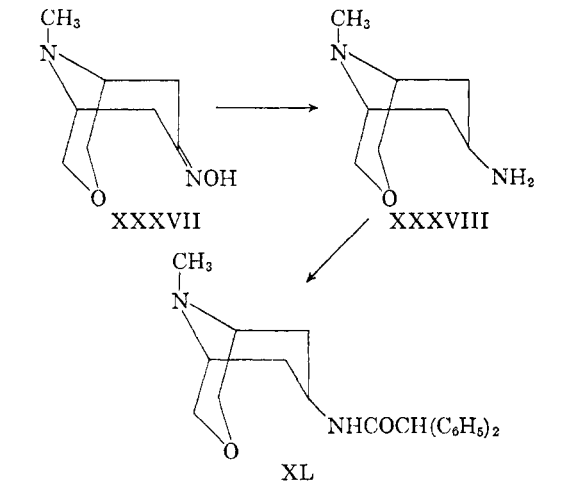


Compound									Carbon, %		Hydrogen, %		Nitrogen, %	
No.	X	R	Config. of OR	Salt	M.P.	Recrystn. Solvent[a]	Formula		Calcd.	Found	Calcd.	Found	Calcd.	Found
XXIII	O	$COC(OH)(C_6H_5)_2$	α	—	82–83[b]	G	$C_{22}H_{25}NO_4$		71.91	71.61	6.86	7.01		
				Picrate	204–205[b]	DA	$C_{28}H_{28}N_4O_{11}$		56.37	56.33	4.73	4.88	9.39	9.39
				Maleate	170–171	A	$C_{26}H_{29}NO_8$		64.58	64.49	6.05	5.96	2.90	3.01
				CH_3Br	234–235	E	$C_{23}H_{28}BrNO_4$		59.74	59.84	6.10	6.27		
XXIV	O	$COC(OH)(C_6H_5)_2$	β	Tartrate	158–160	FC	$C_{26}H_{31}NO_{10}$		60.34	59.97	6.04	5.91		
				CH_3I	215–217	FC	$C_{23}H_{28}INO_4$		54.23	54.03	5.54	5.58		
XXV	O	$CH(C_6H_5)_2$	α	—	87–89	G	$C_{21}H_{25}NO_2$		77.98	78.23	7.79	7.89	4.33	4.38
				HCl	228–230	AB	$C_{21}H_{26}ClNO_2$		70.08	69.78	7.28	7.05		
				CH_3Br	237–239	AB	$C_{23}H_{28}BrNO_2$		63.15	62.77	6.75	6.76		
XXVI	S	$COC(OH)(C_6H_5)_2$	α	HCl	220[c]	AB	$C_{22}H_{26}ClNO_2S\cdot{}^1/_2H_2O$		61.59	61.42	6.34	6.60	3.27	3.53
XXVII	S	$COCH(C_6H_5)_2$	α	HCl	232–233	A	$C_{22}H_{26}ClNO_2S\cdot{}^1/_2H_2O$		63.98	64.19	6.59	6.77	3.39	3.59
XXVIII	S	$CH(C_6H_5)_2$	α	—	175–176	A	$C_{21}H_{25}NOS$		74.29	74.37	7.42	7.60	4.12	4.34
				HCl	205–206	AB	$C_{21}H_{26}ClNOS$		67.09	67.04	6.97	7.13	3.73	3.87
				Picrate	196–196.5	DA	$C_{27}H_{26}N_4O_8S$		57.23	57.34	4.63	5.19	9.89	9.83
XXIX	CH_2	$COC(OH)(C_6H_5)_2$	α	HCl	245 dec.[d]	CB	$C_{23}H_{28}ClNO_3$		68.73	68.53	7.02	6.92		
XXX	CH_2	$COC(OH)(C_6H_5)_2$	β	Citrate	160.5 dec.	CB	$C_{29}H_{35}NO_{10}$		62.46	62.60	6.33	6.50	2.51	2.77
XXXI	CH_2	$CH(C_6H_5)_2$	α	HCl	199–200[e]	AB	$C_{23}H_{28}ClNO$		73.82	73.72	7.89	8.05	3.91	4.05
XXXII	CH_2	$CH(C_6H_5)_2$	β	HCl	232–234	AB	$C_{23}H_{28}ClNO$		73.82	73.91	7.89	8.11	3.91	4.10

[a] Recrystallization solvents: A = ethanol, B = ether, C = methanol, D = acetone, E = acetonitrile, F = butanone, G = petroleum ether (b.p. 30–60°). [b] Jerchel and Weidmann[18] reported this compound. However, the facts that the carbon analysis of the picrate of their material did not agree with theory and that their melting point data are inconsistent with that above cast doubt on the identity of their product. [c] Jerchel and Weidmann[18] reported the free base. [d] Reported in Belgian Patent 555,671: m.p. 242–243°. [e] Reported in Belgian Patent 555,670: m.p. 190–192°.



elsewhere. The benzilic ester of 9-methyl-3-oxagranatanin-7α-ol (XXIII) (SKF No. 5515) is a highly active parasympatholytic agent, exceeding atropine or scopolamine in potency in certain laboratory tests[44]; it is currently undergoing clinical trials as a potential antipeptic ulcer and antiparkinsonism drug.



EXPERIMENTAL[45,46]

Glycolaldehyde dimethyl acetal (XIXa). Benzyloxyacetaldehyde dimethyl acetal[37] (19.6 g., 0.10 mole) in ethanol was hydrogenated over Raney nickel (*ca.* 3 g.) at 60° and an initial pressure of 1400 p.s.i. After removal of the catalyst and solvent the product was distilled through a small Vigreux column; yield 5.5 g. (52%), b.p. 58–60° (12 mm.), n_D^{22} 1.4124 [lit.,[37] b.p. 58–60° (12 mm.), n_D^{25} 1.4118].

In a large run, 333 g. (1.7 moles) of benzyloxyacetal in methanol was reduced over 110 g. of Raney nickel at an initial pressure of 1220 p.s.i. The temperature of the mixture was raised from 25° to 100° over a period of 6 hr. The yield of hydroxyacetal was 133 g. (74%), b.p. 74–77° (31 mm.), n_D^{26} 1.4108.

Glycolaldehyde diethyl acetal (XIXb). By debenzylation of benzyloxyacetaldehyde diethyl acetal[37] at 50–70° as described above the hydroxyacetal, b.p. 72–73.5° (14 mm.), n_D^{21} 1.4152, was obtained in 64% yield [lit.,[37] b.p. 69–70.5° (10 mm.), n_D^{25} 1.4145].

Oxydiacetaldehyde bis(dimethyl acetal) (XXIa). A. To a slurry of 2.48 g. (0.103 mole) of sodium hydride in 20 ml. of xylene in a flask fitted with a condenser (drying tube), mechanical stirrer, and addition funnel was added 10.4 g. (0.098 mole) of hydroxyacetal XIXa. When the initial reaction subsided the mixture was heated at reflux with stirring for 1 hr. The solution was cooled, 18.7 g. (0.15 mole) of dimethylchloroacetal was added, and the resulting mixture was refluxed and stirred for 24 hr. After removal of the precipitated sodium chloride by filtration and concentration of the xylene solution the product, distilled through a small Vigreux column, was obtained as a colorless liquid, b.p. 103–106° (14 mm.), n_D^{21} 1.4166. The yield was 11.9 g. (63%).

B. To a flask, immersed in a Dry Ice–isopropanol bath, and fitted with a stirrer and Dry Ice–condenser, was added 150 ml. of liquid ammonia, 200 ml. of dry ether, and 44.4 g. (0.226 mole) of dimethyl benzyloxyacetal. Sodium was added in small pieces until, after 8.4 g. (0.36 g.-atom) had been added, the color of the solution remained dark blue for 30 min. The ammonia and ether were evaporated, 175 ml. of xylene and 50.5 g. (0.406 mole) of dimethylchloroacetal were added to the residue, and the resulting mixture was stirred and refluxed for 24 hr. Upon working up the reaction mixture as described above, 24.2 g. (55%) of product was obtained, b.p. 106–107° (14 mm.), n_D^{22} 1.4169.

Anal. Calcd. for $C_8H_{16}O_6$: C, 49.47; H, 9.34. Found: C, 49.49; H, 9.64.

Oxydiacetaldehyde bis(diethyl acetal) (XXIb). This compound was prepared according to the procedure above from 4.4 g. (0.033 mole) of hydroxyacetal XIXb, 6.46 g. (0.033 mole) of diethylbromoacetal and 0.80 g. (0.033 mole) of sodium hydride in 100 ml. of toluene. The mixture was stirred and refluxed overnight. The product, obtained in 54% yield, was a colorless liquid, b.p. 81–82° (0.3 mm.), n_D^{24} 1.4158.

Oxydiacetaldehyde bis(2,4-dinitrophenylhydrazone). A mixture of 0.25 g. (0.0013 mole) of oxydiacetal XXIa and 2.5 ml. of water containing 4 drops of acetic acid was refluxed for 30 min. The resulting clear colorless solution was poured into a solution consisting of 0.56 g. of 2,4-dinitrophenylhydrazine, 2.5 ml. of concd. sulfuric acid, 4 ml. of water, and 35 ml. of ethanol. After the mixture had stood for 30 min. at room temperature, the dinitrophenylhydrazone was collected, thoroughly washed with water and then with ethanol, and dried. The orange solid, m.p. 194–196°, weighed 0.56 g. (95%).

(44) J. G. Wilfon and E. Macko, *Federation Proc.*, 18, 458 (1959).

(45) The authors are very grateful to Dr. Walter E. Thompson, Mr. Richard J. Warren, and Miss Barbara Petruzzo (Smith Kline and French Laboratories) for the spectral analyses. They also wish to thank Mrs. Margaret Logan (University of Virginia) and Mrs. Doris Rolston and her staff (Smith Kline and French Laboratories) for the microanalyses.

(46) The authors are indebted to Mr. Elvin L. Anderson, Mr. John E. Casey, Mr. John J. Fitzgerald, Dr. Harold Graboyes, and Dr. Harry E. Reiff for permission to report the results of their large scale preparations of compounds III and IVA and for supplies of the former intermediate.

The same derivative and yield was obtained from oxydiacetal XXIb under the conditions described above.

The analytical sample, m.p. 195–197°, was obtained by recrystallization of the solid from nitromethane.

Anal. Calcd for $C_{16}H_{14}N_8O_9$: C, 41.56; H, 3.05; N, 24.24. Found: C, 41.64; H, 3.29; N, 24.15.

9-Methyl-3-oxagranatanin-7-one (III). A solution of oxydiacetaldehyde was prepared by boiling for 45 min. a mixture of 155 g. (0.80 mole) of oxydiacetal XXIa, 40 ml. of acetic acid, and 150 ml. of water. The clear, almost colorless solution, after cooling, was added to 2 l. of a buffer solution containing 220 g. of disodium phosphate heptahydrate and 75 g. of anhydrous citric acid per liter. Acetonedicarboxylic acid (234 g., 1.60 moles) and 97 g. (1.44 moles) of methylamine hydrochloride were added; the resulting solution was adjusted to *p*H 5 by addition of 40% sodium hydroxide, and water was added to bring the total volume to 4 l. The reaction mixture was kept at 24–28° for 20 hr., the *p*H being maintained at 5.0–5.5 by occasional addition of citric acid. The brown solution was made strongly acidic by addition of concd. hydrochloric acid and extracted with three portions of ether. The aqueous acid solution was then made strongly basic with concd. potassium hydroxide solution and extracted first manually with ten portions of methylene chloride and then continuously for 48 hr. in a liquid-liquid extraction apparatus. From the methylene chloride extracts a total of 87 g. of dark brown oil was obtained. The crude material was dissolved in a minimum volume of methylene chloride and the solution was thoroughly mixed with 350 g. of alumina (20 mesh). By evaporation of the methylene chloride a powder was obtained which was placed in a Soxhlet thimble and extracted with ether for 8 hr. From the ether extract 65 g. of light brown oil was obtained which was crystallized from ether at −20° to yield 38.5 g. (31%) of slightly discolored white needles, m.p. 77–79°. The analytical sample, prepared by recrystallization from ether and sublimation at 70–75° (0.025 mm.), melted at 79–80° (lit.,[18] m.p. 80–82°).

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.95; H, 8.59; N, 9.17.

A *picrate* was obtained from a saturated solution of picric acid in ether and recrystallized from water, m.p. 250° dec.

Anal. Calcd. for $C_{14}H_{16}N_4O_9$: C, 43.75; H, 4.20; N, 14.58. Found: C, 43.88; H, 4.36; N, 14.55.

The *dipiperonylidene derivative*, prepared in ethanol, crystallized as dark yellow needles which, after three recrystallizations from isoamyl alcohol, melted at 232–234°.

Anal. Calcd. for $C_{24}H_{21}NO_6$: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.63; H, 5.32; N, 3.05.

A larger scale run was made in more concentrated solution (388 g., 2.0 moles) of oxydiacetal XXIa, 608 g. (4.16 moles) of acetonedicarboxylic acid and 252 g. (3.14 moles) of methylamine hydrochloride (in a total volume of 6 l.). The dark, oily crude product (223 g.), isolated as described above, was distilled to yield 125 g. of yellow distillate, b.p. 80–100° (0.4 mm.), which partially solidified. A large amount of dark resinous material remained in the distilling flask. The distillate was triturated with two portions of ether to give 92 g. (30%) of white crystals, m.p. 78–79.5°.

From several small scale runs in which the concentrations of reactants were varied or in which the reaction was carried out at *p*H 3, yields of 20–25% of ketone were obtained.

Thiodiacetaldehyde bis(dimethyl acetal). A mixture of 1150 g. (4.8 moles) of sodium sulfide nonahydrate, 54.7 g. of potassium iodide, 397 g. (3.19 moles) of dimethylchloroacetal, 1 l. of water and 2.1 l. of 95% ethanol was stirred under reflux for 24 hr. About 2.5 l. of solvent was distilled from the mixture, the remaining aqueous solution was saturated with potassium carbonate and extracted with several portions of ether. From the ether extracts, dried over sodium sulfate, was obtained 266 g. (79%) of product, b.p. 80–84° (0.8 mm.), n_D^{21} 1.4573 [lit.,[47] b.p. 85° (1 mm.), n_D^{25} 1.4569].

The *bis(2,4-dinitrophenylhydrazone) of thiodiacetaldehyde* was obtained in 91% yield from a solution of the aldehyde prepared by warming a mixture of 1.0 g. of the diacetal and 5 ml. of water containing 1 drop of concd. hydrochloric acid. After recrystallization from dimethylformamide-methanol the derivative melted at 219–221° (lit.,[48] m.p. 216°).

9-Methyl-3-thiagranatanin-7-one (V). Thiodiacetaldehyde bis(dimethylacetal) (265 g., 1.26 moles) was hydrolyzed in 700 ml. of hot water containing 12 ml. of concd. hydrochloric acid. To the clear solution, cooled to 25°, was added 94 g. (1.39 moles) of methylamine hydrochloride and 220 g. (1.51 moles) of acetonedicarboxylic acid. The mixture was stirred and solid potassium carbonate was added slowly until the *p*H of the solution was 3.0. The clear solution was allowed to stand at room temperature in the dark, the *p*H being held between 3.0 and 3.5 by addition of hydrochloric acid after 2 hr. and after 7 hr. After 24 hr. the dark brown solution was acidified to *p*H 2 with 6*N* hydrochloric acid and extracted with four portions of ether. The aqueous solution was then made strongly alkaline, saturated with potassium carbonate, and extracted with seventeen portions of methylene chloride. The combined extracts were dried over sodium sulfate, concentrated to about 200 ml. and thoroughly mixed with alumina (20 mesh) to give, after evaporation of solvent, a brown powder which was placed in a Soxhlet thimble and extracted with ether. From the ether extracts a dark crystalline solid was obtained which on sublimation *in vacuo* afforded 62 g. (29%) of product, m.p. 124–128°. A sample recrystallized from benzene-ligroin melted at 126–128° (lit.,[17] m.p. 126–127°). The dipiperonylidene derivative melted at 240–242° (lit.,[17] m.p. 241°).

No improvement in yield resulted in smaller scale experiments carried out in buffered solutions at *p*H 3, in considerably more dilute solutions, or in solutions containing a greater excess of acetonedicarboxylic acid. A slightly lower yield was obtained when the reaction was run at *p*H 4–5.

9-Methyl-3-oxagranatanin-7α-ol (IVA). A. Three grams (0.0194 mole) of 9-methyl-3-oxagranatanin-7-one in 50 ml. of glacial acetic acid was hydrogenated in the presence of 0.15 g. of ruthenium oxide at an initial hydrogen pressure of 1080 p.s.i. The temperature was raised to 90° over a period of 6 hr. The solution, after removal of the catalyst, was concentrated, treated with alkali, and extracted with methylene chloride. From the extract, after drying over sodium sulfate and removal of solvent, was obtained a waxy solid which crystallized on trituration with ether and petroleum ether. The product, m.p. 141–143°, weighed 2.4 g. (79%). A sample after sublimation and recrystallization from petroleum ether (b.p. 30–60°) melted at 144–146°.

B. The ketone (62 g., 0.40 mole) in 1 l. of ethanol was hydrogenated in the presence of 15–20 g. of Raney nickel at 19–65° at an initial pressure of 1000 p.s.i. The reduction was essentially completed in 4 hr. The crude product, a white waxy solid, was recrystallized from 150 ml. of petroleum ether (b.p. 30–60°) to give 55 g. of white flakes, m.p. 140–143°. From the filtrate was obtained a second crop of crystals, 4.5 g., m.p. 139–142°. The total yield was 59.5 g. (95%).

C. In a flask equipped with a stirrer and a Soxhlet extractor was placed 27.0 g. (0.693 mole) of lithium aluminum hydride and 1500 ml. of ether. As the mixture was stirred and refluxed 85.9 g. (0.554 mole) of ketone was washed from the Soxhlet thimble into the reaction flask. After the mixture was stirred and refluxed for 9 hr. it was decomposed by the gradual addition of 51 ml. of water. The ether layer was decanted from the inorganic solid, the latter was washed

(47) W. E. Parham, H. Wynberg, and F. L. Ramp, *J. Am. Chem. Soc.*, **75**, 2065 (1953).

(48) F. Weygand, G. Eberhardt, H. Linden, F. Schäfer, and I. Eigen, *Angew. Chem.*, **65**, 525 (1953).

thoroughly with ether, and the combined ether solutions were dried over potassium carbonate. Upon evaporation of the solvent 82.0 g. (94%) of white waxy solid, m.p. 138–144°, was obtained. The product, after recrystallization from petroleum ether, melted at 144–145°.

The *picrate* was prepared in water; the *tartrate*, *methobromide*, and *methiodide* were formed in acetone solution.

The infrared spectrum of IVA showed characteristic bands at 9.0 (s), 9.95 (m), 10.05 (m), and 10.9 (s) μ.

In a known mixture of 90% of IVA and 10% of its epimer IVB, the latter isomer was readily detected by the presence of peaks at 10.35, 11.2, and 11.75 μ (see below) in the spectrum of the mixture (chloroform solution). In the spectra of the crude products obtained from ketone III by reduction with lithium aluminum hydride and by catalytic hydrogenation, these peaks were of lower intensity than those in the spectrum of the known mixture, indicating that the former mixtures contained less than 10% of IVB and, by difference, 90% or more of IVA. Allowing for small amounts of impurities, including ketone (the spectra exhibited very little or no carbonyl absorption at 5.9 μ), possibly present in the mixtures, a reasonable estimate of the proportion of IVA in the reduction products is >85%.

9-Methyl-3-oxagranatanin-7β-ol (IVB). A. Sodium (60 g.) was added in small pieces to a refluxing, vigorously stirred solution of 25 g. (0.16 mole) of 9-methyl-3-oxagranatanin-7-one in 1500 ml. of 1-pentanol. Water and then hydrochloric acid were added to the cooled solution and the pentanol layer was repeatedly extracted with 6*N* hydrochloric acid. The combined acidic aqueous extracts were extracted with three portions of ether, made alkaline with concd. potassium hydroxide, and saturated with potassium carbonate. Continuous extraction of the mixture with chloroform gave, on evaporation of the dried solution, 24 g. (95%) of colorless solid, m.p. 106–110°. The product after recrystallization from benzene melted at 111–113° (19.5 g., 78% yield). Further recrystallizations and sublimation only slightly raised the melting point.

The *picrate* precipitated from a saturated solution of picric acid in ethanol. The *methiodide* was prepared in ethanol.

The infrared spectrum of IVB exhibited characteristic absorption at 9.0 (w), 9.2 (m), 10.35 (s), 11.2 (w), and 11.75 (m) μ.

In the spectrum of a known mixture of 90% of IVB and 10% of IVA in chloroform solution the bands at 9.0, 9.95, 10.05, and 10.9 μ attributed to the latter epimer were easily recognized. Since these bands were missing in the spectra of the first fraction of the sodium-pentanol reduction product, m.p. 111–113°, and of second crops, m.p. 108–112° (which together accounted for over 80% of the total product), the proportion of IVB in the crude reduction mixture was estimated to be >80%.

B. *By epimerization of* IVA. A solution of 5.00 g. of IVA, 7.2 g. of aluminum isopropoxide, and 1.7 ml. of dry acetone in 170 ml. of dry 2-propanol was refluxed for 308 hr. The 2-propanol was removed *in vacuo*, the residue was dissolved in 10% sodium hydroxide solution, and the latter was saturated with potassium carbonate. The mixture was thoroughly extracted with ether and the extracts were dried over potassium carbonate. On evaporation of the solvent 4.75 g. of white, hygroscopic solid melting at 70–100° was obtained.

Spectral analysis of the product as described above indicated that it contained more than 10% of IVA. Recrystallization of 4.45 g. of the mixture from benzene gave 2.60 g. (58% recovery) of essentially pure IVB, m.p. 108–111°. Further recrystallization of the material yielded the pure epimer m.p. 111.5–113°.

When the epimerization was carried out for 96 hr. using 5 g. of aluminum isopropoxide, IVB was isolated in very poor yield.

9-Methyl-3-oxagranatanin-7β-ol benzoate. A mixture of 0.3 g. of 9-methyl-3-oxagranatanin-7β-ol (IVB) and 0.4 g. of benzoyl chloride was heated at 130–150° for 2 hr. The brown crystalline mass was dissolved in 3*N* hydrochloric acid and the solution was extracted with ether. The acid solution was made alkaline, saturated with sodium carbonate, and extracted with chloroform to give, after removal of the solvent, 0.5 g. of crystalline product, m.p. 103–105°.

9-Methyl-3-oxagranatanin-7α-ol benzoate. From the reaction of 0.2 g. of 9-methyl-3-oxagranatanin-7α-ol (IVA) with benzoyl chloride under the conditions described above, 0.25 g. of product, m.p. 76–78°, was obtained.

9-Methyl-3-thiagranatanin-7α-ol (VIA). Ketone V (25.0 g., 0.146 mole) was reduced with 6.1 g. (0.16 mole) of lithium aluminum hydride in 225 ml. of ether by the procedure described above for reduction of the oxaketone III. The mixture was stirred and refluxed for 15 hr. The crude product weighed 22.9 g. (91%), m.p. 93–98°. Recrystallization of 5.0 g. of this material once from ligroin and twice from benzene–petroleum ether (b.p. 30–60°) gave 2.1 g. of the α-ol, m.p. 108–110°.

The *picrate* precipitated from an ether solution of picric acid; the *methiodide* was formed in acetone.

A sample (2.1 g.) of the residue from the mother liquors of the α-ol was chromatographed on alumina. From the benzene eluates fractions melting in the range of 90° to 100° were obtained (total wt. 1.0 g.) which on recrystallization from ether yielded the α-ol. Benzene-chloroform (9:1) eluates contained lower melting fractions. From the chloroform eluates was obtained 0.3 g. of the β-ol, m.p. 113–115°, which was raised to 115.5–116.5° on recrystallization of the sample from benzene-petroleum ether.

The infrared spectrum of VIA showed characteristic peaks at 8.9 (m), 9.2 (s), 9.7 (w), 10.1 (m), 10.65 (m), 11.2 (s), and 11.3 (s) μ.

On the basis of a spectral analysis of the crude reduction product similar to that described above for mixtures of IVA and IVB, using the absorption peaks at 9.7, 10.5, and 10.85 μ to detect the presence of epimer VIB (see below), the proportion of VIA in the mixture was estimated to be >85%.

9-Methyl-3-thiagranatanin-7β-ol (VIB). Sodium-pentanol reduction of 3.65 g. (0.0214 mole) of ketone V was carried out in the way described above using 8.5 g. of sodium and 220 ml. of 1-pentanol. The crude product, m.p. 97–110°, weighed 3.5 g. (95%). After sublimation and recrystallization from benzene the material melted at 102–108°. Chromatography of a sample (1.7 g.) on alumina gave, from the benzene eluate, 0.09 g. of solid melting at 103–116.5°, and, from the benzene-chloroform (95:5) eluate, 1.25 g. of essentially pure β-ol, m.p. 115–117°. By recrystallization of the latter fraction from benzene the pure compound, m.p. 116.5–117°, was obtained.

The *picrate* was prepared in aqueous ethanol and the *methiodide* in acetone.

Characteristic peaks in the infrared spectrum of VIB were at 8.85 (w), 9.7 (s), 10.5 (w), and 10.85 (w) μ.

The fraction of reduction product, m.p. 102–108°, and a second crop, m.p. 100–108°, were subjected to spectral analysis as described above, using the peaks at 9.2 and 10.1 μ to detect the presence of epimer VIA. These peaks were missing in the spectra of both fractions (which represented 80% of the total product) although they were clearly exhibited in the spectrum of a known mixture of the epimers containing 10% of VIA. From these data the proportion of VIB in the crude reduction mixture was estimated to be >75%.

9-Methylgranatanin-3α-ol (VIIIA). A solution of 10.0 g. (0.0655 mole) of pseudopelletierine[40] (VII) in 150 ml. of ether was added during 10 min. to a mixture of 1.24 g. (0.0327 mole) of lithium aluminum hydride and 200 ml. of ether. The mixture was stirred and refluxed for 6 hr. and worked up in the way described above. The crude product, a hygroscopic, low-melting solid, weighing 9.35 g. (92%). Recrystallization of the material from petroleum ether

(b.p. 30–60°) gave VIIIA, m.p. 69° (lit.,[28] m.p. 69°), identical with a sample prepared by hydrogenation of pseudopelletierine over Raney nickel according to Alder and Dortmann.[28]

The crude products from the lithium aluminum hydride reduction and the catalytic hydrogenation both yielded picrates having m.p. 275° which was unchanged by recrystallization of the salts from ethanol (lit.,[28] m.p. 275–276°).

Both crude alcohols gave the same methiodide, m.p. 339° dec., from acetone solution in 94% yield. The two samples of the salt, after recrystallization from methanol, melted at 344° dec.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.41; H, 6.78; N, 4.71. Found: C, 40.29; H, 6.89; N, 4.90.

The infrared spectrum of VIIIA exhibited characteristic bands at 8.82 (m), 9.0 (s), 9.5 (s), 9.85 (s), 10.0 (m), and 10.5 (w) μ.

On the basis of a spectral analysis of the crude reduction product similar to that described above for mixtures of IVA and IVB, using the absorption peaks at 9.6 and 10.3 μ to detect the presence of epimer VIIIB (see below), the proportion of VIIIA in the mixture was estimated to be >85%.

9-Methylgranatanin-3β-ol (VIIIB). This alcohol was prepared according to the directions of Alder and Dortmann[28]; m.p. 98–99° (lit.,[28] m.p. 99–100°). The picrate melted at 264–265° (lit.,[28] m.p. 264–265°).

The methiodide, prepared in acetone solution, melted at 329° dec. after recrystallization from methanol.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.41; H, 6.78; N, 4.71. Found: C, 40.26; H, 6.84; N, 5.12.

The infrared spectrum of VIIIB showed characteristic peaks at 8.82 (s), 9.0 (m), 9.15 (w), 9.6 (s), 10.1 (m), and 10.3 (m) μ.

3-Oxagranatanin-7β-ol (XIVB) *and 7α-ol* (XIVA). Following the procedure of Ciamician and Silber,[49] 2.4 g. (0.015 mole) of potassium permanganate in 120 ml. of water was added dropwise during 45 min. to a stirred solution of 1.1 g. (0.007 mole) of 9-methyl-3-oxagranatanin-7β-ol (IVB) or 7α-ol (IVA) and 1.1 g. of potassium hydroxide in 50 ml. of water. The reaction mixture was maintained at 0–5° during the addition and for an additional hour. After standing overnight at 25°, the mixture was filtered through Celite and the filtrate was continuously extracted with chloroform for 48 hr. to isolate the product.

From IVB 0.9 g. (90%) of crude *nor* base XIVB, m.p. 125–129°, was obtained. The picrate was prepared in ethanol.

From IVA 1.0 g. (100%) of crude *nor* base XIVA, m.p. 199–205°, was obtained. The *picrate* was formed in ether.

Methylation of XIVB and XIVA with formaldehyde and formic acid according to the procedure of Nickon and Fieser[38] gave 9-methyl-3-oxagranatanin-7β-ol (IVB), m.p. 111–113°, and 7α-ol (VA), m.p. 143–145°, respectively, proving that no change in the ring system of the alcohols occurred in the permanganate oxidation.

9-Benzoyl-3-oxagranatanin-7β-ol (XVB) *and 7α-ol* (XVA). These derivatives were prepared from 3-oxagranatanin-7β-ol (XIVB) and 7α-ol (XIVA) by the Schotten-Baumann procedure.[50]

Amide XVB, m.p. 143–144°, exhibited strong bands in the infrared spectrum (potassium bromide disc) at 2.93, 6.19, and 6.34 μ.

Amide XVA, m.p. 131–133°, showed major peaks in its infrared spectrum (potassium bromide disc) at 2.96, 6.19, and 6.28 μ.

3-Oxagranatanin-7β-ol benzoate (XVIB) *and 3-oxagranatanin-7α-ol benzoate* (XVIA). These esters were prepared by heating the hydrochloride salts of 3-oxagranatanin-7β-ol (XIVB) and 7α-ol (XIVA) with excess benzoyl chloride at 120–130° for 1.5 hr. The crude hydrochlorides of the amino esters thus obtained were treated with ammonium hydroxide to liberate the bases which were isolated by chloroform extraction of the basic mixtures.

The infrared spectrum of amino ester XVIB, m.p. 115–117°, showed a strong band at 5.84 μ and that of its epimer XVIA, m.p. 106–108°, exhibited a strong band at 5.85 μ.

Benzoyl migration (*N* → *O*). A solution of 0.3 g. of XVB in 15 ml. of dry dioxane saturated with hydrogen chloride was allowed to stand at room temperature for 56 hr. Evaporation of the solvent gave a hydrochloride salt, m.p. 215–220°, which by treatment with ammonium hydroxide was converted to a base, m.p. 108–117°. After recrystallization from benzene-petroleum ether (b.p. 30–60°) the latter melted at 115–117° and was shown to be identical with XVIB by its infrared spectrum and mixture melting point.

When XVA was treated as described above it was recovered unchanged. The spectrum and melting point of the recovered material were identical with those of XVA.

Benzoyl migration (*O* → *N*). Ester XVIB (0.05 g.) was dissolved in a small volume of dilute hydrochloric acid and the solution was adjusted to *p*H 10 by addition of 5% sodium hydroxide. After standing 30 min. at 28° the solution was extracted with chloroform. From the dried chloroform extract was obtained a solid, m.p. 141–144°, which was shown to be identical with amide XVB.

No acyl migration occurred when the epimeric ester XVIA was treated as described above. The infrared spectrum of the crude product, melting at 100–208°, showed no amide band at 6.19 μ and the low intensity of the ester peak at 5.85 μ indicated that the ester had been hydrolyzed to a large extent.

Tetrahydrooxazine derivative of 3-oxagranatanin-7β-ol (XVII). Following the procedure of Hardegger and Ott[51] this derivative was prepared from 0.15 g. of 3-oxagranatanin-7β-ol (XIVB) and 0.16 g. of *p*-nitrobenzaldehyde. The product, after two recrystallizations from ether, melted at 157–157.5°.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84. Found: C, 60.89; H, 6.17.

Under the same conditions the epimer (XIVA) gave no crystalline tetrahydrooxazine derivative. The dark brown oily product could not be purified.

Preparation of benzilates XXIII, XXIV, XXVI, XXIX, *and* XXX (*Table III*). These esters were prepared according to the general procedure of Stoll *et al.*[52] The following description of the preparation of 7α-benziloyloxy-9-methyl-3-oxagranatanine exemplifies the method.

A mixture of 10.0 g. (0.0637 mole) of 9-methyl-3-oxagranatanin-7α-ol (IVA) (crude product from catalytic hydrogenation of ketone III), 33.2 g. (0.137 mole) of methyl benzilate and 0.25 g. of sodium was heated at 120–125° at 0.6 mm. pressure for 30 hr. The red glass obtained was taken up in 95 ml. of 10% hydrochloric acid and the mixture was extracted with ether. On addition of concd. ammonium hydroxide to the acidic aqueous solution a thick gum separated which was removed by extraction with chloroform. The chloroform solution was thoroughly washed with water, dried over sodium sulfate, and evaporated to give 13.4 g. (58%) of crude ester as a red glass. The crystalline maleate salt, prepared in acetone, was obtained in 85% yield. From the maleate, by treatment with alkali, the pure ester base was obtained as a white crystalline solid.

The *picrate* was formed in ethanolic picric acid solution; the *methobromide* was prepared in acetone.

In a similar way the following esters were prepared:

7β-Benziloyloxy-9-methyl-3-oxagranatanine (XXIV), obtained from IVB in almost quantitative yield as a red-brown

(49) G. Ciamician and P. Silber, *Ber.*, 27, 2850 (1894).

(50) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 1948, p. 88.

(51) E. Hardegger and H. Ott, *Helv. Chim. Acta*, 36, 1186 (1953).

(52) A. Stoll, E. Jucker, and A. Lindenmann, *Helv. Chim. Acta*, 37, 495 (1954).

glass; the *tartrate* was prepared from equimolar amounts of the base and tartaric acid in methanol-acetone solution.

7α-Benziloyloxy-9-methyl-3-thiagranatanine (XXVI), from VIA as a thick oil in 55% yield; the *hydrochloride* was precipitated from an ether solution of hydrogen chloride.

3α-Benziloyloxy-9-methylgranatanine (XXIX), from VIIIA as a thick oil in 44% yield; the *hydrochloride* was prepared in ether.

3β-Benziloyloxy-9-methylgranatanine (XXX), from VIIIB as a glass in 45% yield; the *citrate* was prepared from equimolar quantities of the base and citric acid in acetone-ether solution.

Preparation of benzhydryl ethers XXV, XXVIII, XXXI, *and* XXXII (*Table III*). The following method for preparing *7α-benzhydryloxy-9-methyl-3-oxagranatanine* (XXV) from amino alcohol IVA illustrates the general procedure used in preparing all of the benzhydryl ethers.

A solution of 2.00 g. (0.0127 mole) of alcohol IVA (crude product from hydrogenation of ketone III), 2.34 g. (0.0127 mole) of dry tributylamine, and 5.15 g. (0.0254 mole) of benzhydryl chloride in 15 ml. of dry dimethylformamide was refluxed for 8 hr. The brown solution was concentrated *in vacuo* to about one half its original volume, three volumes of ether were added, and the resulting mixture was stored at −20°. The crude hydrochloride salt of the benzhydryl ether which separated weighed 4.60 g. (98.5%), m.p. 215°. By trituration of this material with cold acetone 3.80 g. (84%) of white crystals, m.p. 232–234°, was obtained. Two recrystallizations of the hydrochloride from ethanol-ether did not change the melting point. From the salt a base, m.p. 86–89°, was obtained, which, after recrystallization from petroleum ether (b.p. 30–60°), melted at 87–89°.

Using the crude alcohol IVA from the lithium aluminum hydride reduction of ketone III, the same benzhydryl ether hydrochloride, m.p. 232–234°, and base, m.p. 87–89°, were obtained, again in 84% yield. That the benzhydryl ethers from the two samples of alcohol IVA were identical was demonstrated by the mixture melting point method and by the fact that the infrared spectra of the two samples of base were identical in all respects as were those of their hydrochlorides.

The *methobromide* salt of XXV was prepared in acetone.

In a similar way the following compounds were prepared: *7α-benzhydryloxy-9-methyl-3-thiagranatanine* (XXVIII) *hydrochloride*, in 48% yield; *3α-benzhydryloxy-9-methylgranatanine* (XXXI) *hydrochloride*, in 63% yield; and *3β-benzhydryloxy-9-methylgranatanine* (XXXII) *hydrochloride*, in 82% yield.

9-Phenylacetyl-3-oxagranatanin-7β-ol (XXXIII). To a vigorously stirred solution of 2.0 g. (0.014 mole) of 3-oxagranatanin-7β-ol (XIVB) and 5.9 g. of potassium carbonate in a mixture of water (20 ml.), chloroform (10 ml.), and methanol (10 ml.) was added 6.6 g. (0.043 mole) of phenylacetyl chloride over a period of 20 min. Then 5 ml. of 10% potassium hydroxide was added and stirring was continued for 3 hr. The mixture was diluted with water and extracted with chloroform. From the dried chloroform solution was obtained 3.5 g. (94%) of solid melting at 141–150°. The pure product, m.p. 158–159.5°, was obtained after three recrystallizations of the material from benzene-ligroin.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 68.83; H, 7.13.

9-Phenethyl-3-oxagranatanin-7β-ol (XXXIV). A mixture of 1.8 g. (0.0069 mole) of 9-phenylacetyl-3-oxagranatanin-7β-ol (XXXIII) (introduced from a Soxhlet thimble), 1.7 g. (0.042 mole) of lithium aluminum hydride and 500 ml. of ether was stirred and refluxed for 11 hr. Water and then 6*N* hydrochloric acid were added to the reaction mixture. The ether layer was separated and extracted with four portions of 3*N* hydrochloric acid. The combined acidic aqueous solutions were made strongly alkaline and extracted repeatedly with chloroform. From the chloroform solution, after drying over sodium sulfate, was obtained 1.15 g. (68%) of product, m.p. 83–85°. The analytical sample, obtained after two recrystallizations of the material from ligroin, had the same m.p.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.88; H, 8.36.

7β-Benzhydryloxy-9-phenethyl-3-oxagranatanine (XXXV). This compound as its hydrochloride was obtained in very poor yield from the reaction of benzhydryl chloride with amino alcohol XXXIV, carried out according to the procedure described above. The salt, after several recrystallizations from butanone-methanol-ether, melted at 199–201.5°.

Anal. Calcd. for $C_{29}H_{32}ClNO_2$: C, 74.73; H, 7.17. Found: C, 74.32; H, 7.27.

9-Methyl-7-phenyl-3-oxagranatanin-7-ol (XXXVI). A solution of 4.0 g. (0.026 mole) of 9-methyl-3-oxagranatanin-7-one (III) in ether was added to a solution of phenyllithium, prepared from 6.5 g. (0.041 mole) of bromobenzene and 0.82 g. (0.12 g.-atom) of lithium, in 75 ml. of ether and the resulting mixture was stirred under reflux for 4 hr. Water was added and the ether layer was removed, washed with ammonium hydroxide and water, and dried over sodium sulfate. The product obtained from the ether solution was a somewhat waxy solid weighing 3.4 g. (57%). Recrystallization of the material from petroleum ether (b.p. 30–60°) containing a small amount of ethyl acetate gave white crystals melting at 129–132°. The picrate, recrystallized from ethanol-acetone, melted with decomposition at 207°.

Anal. Calcd. for $C_{22}H_{22}N_4O_9$: C, 51.95; H, 4.80. Found: C, 51.93; H, 4.62.

9-Methyl-3-oxagranatanin-7-one oxime (XXXVII). A solution of 6.0 g. (0.039 mole) of ketone III, 12 g. of hydroxylamine hydrochloride, and 12 g. of potassium hydroxide in 100 ml. of water was heated at 70° for 6 hr. After standing at room temperature for 18 hr. the solution was saturated with sodium carbonate and repeatedly extracted with chloroform. From the dried extract was obtained 6.0 g. (91%) of crystalline solid, m.p. 165–167°. The analytical sample, obtained by recrystallization of the product from ethyl acetate, melted at 168.5–169.5°.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 56.45; H, 8.29. Found: C, 56.44; H, 7.97.

7β-Amino-9-methyl-3-oxagranatanine (XXXVIII). To a refluxing and well stirred solution of 4.0 g. (0.024 mole) of 9-methyl-3-oxagranatanin-7-one oxime (XXXVII) in 300 ml. of 1-pentanol was added 12 g. of sodium in small pieces over a period of 30 min. After an additional 30 min. of heating, the solution was cooled, water was added, and the resulting mixture was made acidic by addition of 6*N* hydrochloric acid. The pentanol layer was withdrawn and extracted five times with 6*N* acid. The combined acid solutions, after extraction with ether, were made alkaline, saturated with potassium carbonate, and extracted repeatedly with chloroform. The product obtained from the chloroform solution was a colorless oil, 4.0 g., b.p. 86° (2.5 mm.), which solidified to a waxy solid. The *phenylthiourea derivative*, prepared in methanol and recrystallized once from benzene and three times from butanone, melted at 155–157°.

Anal. Calcd. for $C_{16}H_{21}N_3OS$: C, 61.82; H, 7.26; N, 14.42. Found: C, 61.77; H, 7.39; N, 14.10.

7β-(2,2-Diphenylacetamido)-9-methyl-3-oxagranatanine (XL). A solution of 1.63 g. (0.007 mole) of diphenylacetyl chloride in 25 ml. of benzene was added over a period of 30 min. to a stirred suspension of 1.05 g. (0.0067 mole) of amine XXXVIII and 0.7 g. of powdered sodium carbonate in 25 ml. of benzene. The mixture was stirred at room temperature for 4.5 hr. and at 50–60° for 1 hr. Sodium carbonate solution was added and the mixture was extracted four times with chloroform. After evaporation of the solvent, 2.55 g. of solid, m.p. 178–188°, was obtained. The product, after four recrystallizations from ethyl acetate, melted at 195–196°.

Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.57; H, 7.37; N, 7.56.

CHARLOTTESVILLE, VA.
PHILADELPHIA, PA.